The case-control design does not provide an estimate of disease incidence in vaccinees and nonvaccinees, therefore, the RR component of the PE formula is not directly calculable. However, when the disease outcome for the study is rare or when suitable sampling strategies are used for selecting cases and controls (100), the RR from a controlled cohort design is approximated by the odds ratio (OR) of vaccination in cases versus controls, where OR = (odds of vaccination in cases)/(odds of vaccination in controls) and PE = (1 − OR) × 100%.

Because cases are defined only on the basis of one disease outcome, a case-control study can evaluate only one outcome of vaccination. However, with a well-focused research hypothesis, case-control studies can enable powerful assessments of vaccine performance in practice. For example, recent case-control studies have provided useful post-licensure evaluations of vaccine protection against such rare diseases as invasive pneumococcal (5) and Hib (101) infections. In addition, this design has proved extremely useful in evaluating rare but serious potential side effects, such as Guillain-Barré syndrome following vaccination with swine influenza vaccine and serious pediatric neurological syndromes following vaccination with conventional whole-cell pertussis vaccine (89,102).

Variant designs. It has been proposed that vaccine performance can sometimes be assessed in the context of prevalence surveys designed primarily to assess vaccine coverage of a target population (82). At the time of the survey, respondents are asked about the date of past vaccination as well as the date of intervening disease and vaccine protection is calculated as if a conventional controlled cohort study had been done on vaccinees versus nonvaccinees. This design differs from a conventional controlled cohort study in that it evaluates only those members of the original cohorts of vaccines and nonvaccinees who are still present at the time of the survey. It thereby ignores cohort members who have migrated out or died during the interval before the survey. Consequently, this design is sometimes referred to as a ''residue cohort.''

Routine statistics on vaccine coverage can also be used to serve as control groups in assessments of vaccine protection. It has, for example, been proposed that vaccine coverage ascertained for a representative series of cases can be compared with routinely available estimates of vaccine coverage for the source population for the cases as a tactic to monitor vaccine protection on a routine basis (103). ORs of vaccination in the case group relative to the source group are calculated, and the expression (1 − OR) × 100% estimates vaccine protection. If ''signals'' of inadequate protection emerge from such screening studies, these studies can then be followed up by more rigorous cohort or case-control studies of vaccine protection.

An interesting hybrid design was developed to assess pneumococcal polysaccharide vaccine protection (104). In this design, isolates from cases of invasive pneumococcal disease sent to a referral center were typed and histories of antecedent vaccination were obtained without knowledge of these types. Since conventional pneumococcal polysaccharide vaccine contains only a fraction of pneumococcal serotypes encountered in infected patients and since serotypes contained in the vaccine are not expected to protect against infections caused by other serotypes, the nonvaccine serotype infections can be considered a suitable control group for the vaccine serotype ''cases,'' and the expression (1 − OR) × 100% estimates vaccine protection.

Finally, because it is sometimes necessary to evaluate putative vaccine side effects in situations in which vaccine coverage is very high, leaving very few unvaccinated subjects for comparison, an innovative design, termed ''case-series,'' has been used. In this design, the incidence of the adverse event of interest is compared within two windows of time for the same subject: a ''vaccine window,'' an interval after dosing during which vaccine-related side effects are postulated to occur; and a ''control window,'' an interval proximate to dosing during which vaccine-related side effects are postulated not to occur. The ratio of these two incidence rate estimates is taken to estimate the relative rate and/or risk of the event in vaccinees relative to nonvaccinees. This is analogous to crossover designs used in RCTs, in which the essential comparison is the within-subject occurrence of the target outcome before and after the crossover from one agent to another. This design, which can be used to study acute, transient adverse effects that occur during a predictable time window shortly after vaccination, was used very successfully in the evaluation of intussusception following oral receipt of live rhesus rotavirus reassortant vaccine and produced estimates of the relative risk of this outcome in vaccinees versus nonvaccinees that were quite similar to estimates from case-control studies (105).

Increasing Importance of Population-Based Databases

Recent years have witnessed an explosion of allegations about putative serious side effects associated with receipt of vaccines. Some of these alleged associations, such as the occurrence of intussusception following oral receipt of live rhesus rotavirus reassortant vaccine, have been verified by credible scientific studies (105,106). Others, such as the alleged occurrence of inflammatory bowel disease or autism following MMR vaccine, have not been substantiated (107,108). Because assertions about vaccine safety can threaten public confidence in vaccines used in routine practice, it has been proved essential that credible, suitably controlled studies be completed rapidly when such assertions arise. In the past, public health systems relied principally on side effects voluntarily reported by individual physicians. An example of such a system is the Vaccine Adverse Event Reporting System (VAERS) managed by the U.S. Public Health Service (109). Because of the selective and incomplete reporting of side effects inherent in these systems, as well as uncertainties about the denominators of vaccinees at risk and the occurrence of target side effects in nonvaccinees, special large-linked, computerized databases have been created, such as the Vaccine Safety Datalink (VSD) created by the U.S. Centers for Disease Control (110). These databases link histories of receipt or nonreceipt of vaccines in a defined population with comprehensive records of treatment encounters and hospitalizations for specific outcome conditions in the same population. In addition, information about demographic and socioeconomic variables for each subject is collected to permit control for possible confounders in analyses of vaccine-adverse event associations. If maintained for a suitably large cohort of the target population, these databases enable rapid, controlled analyses and provide the public health community with the evidence necessary for proper regulation of the usage of licensed vaccines. Unfortunately, although such databases are becoming increasingly common in industrialized countries, they are virtually nonexistent in developing countries (111). One large-linked, dynamic database to evaluate vaccine safety issues has been piloted in Vietnam, but there is a pressing need to develop more such systems in the developing world (112).